

### REMARKS

Claims 34-37, 39, 41-52, 55-77, 79, 81-90, 101, and 102 are pending in the application and stand rejected. Claims 34, 74, 101, and 102 have been amended. Claims 39, 41-52, 55, 56, 70-73, 79, and 81-90. Reconsideration and allowance of Claims 34-37, 57-69, 74-77, 101, and 102 is respectfully requested.

### Telephone Conference

Applicants note with appreciation the telephone conference with the Examiner on June 19, 2003 in which the Examiner made helpful suggestions for placing the application in condition for allowance. After the telephone interview with the Examiner, applicants' attorney discussed the substance of the telephone conference with the applicants. However, applicants were unable to formulate a response before the Examiner was required to issue the present Examiner's Action. Applicants believe that the above claim amendments and following remarks address the Examiner's concerns expressed in the telephone conference and place the application in condition for allowance. Applicants respectfully request entry of this amendment.

### The Rejection of Claims 34, 35, 37, 38, 41-43, 47,

### 48, 50, 66, 68, 70-75, 77, 79, 81, and 83-86 Under 35 U.S.C. § 102(b)

Claims 34, 35, 37, 38, 41-43, 47, 48, 50, 66, 68, 70-75, 77, 79, 81, and 83-86 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 93/14142. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Of these rejected claims, Claims 34 and 74 are independent and relate to methods and compositions, respectively, that include a therapeutic or diagnostic agent, and a transport agent that is a poly(carboxylic acid) polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5. The cited reference describes the use of copolymers, acrylic acid and methylacrylic acid. Claims 34 and 74 have been amended to recite that the polymer is

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selected from the group consisting of poly(ethylacrylic acid), poly(propylacrylic acid), poly(butylacrylic acid), and mixtures thereof.

Because the cited reference fails to describe the invention as now claimed, the reference is not anticipatory, and withdrawal of this grounds for rejection is respectfully requested. Applicants further submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed.

The Rejection of Claims 34-37, 39, 41-43, 47-50,  
57-59, 64-77, 79, 81, and 83-86 Under 35 U.S.C. § 102(a)

Claims 34-37, 39, 41-43, 47-50, 57-59, 64-77, 79, 81, and 83-86 stand rejected under 35 U.S.C. § 102(a) as being anticipated by WO 97/09068. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Of these claims, Claims 34 and 74 are independent and, as noted above, have been amended. WO 97/09068 describes a site-specific conjugate that includes a stimuli-responsive polymer coupled to a recognition biomolecule. See Abstract. The cited reference describes drug delivery applications at page 52, line 19 through page 54, line 4. The reference describes delivery of a drug into a cell, within an endosome, where the drug is released inside the endosome, where the linkage of the polymer to the drug is labile. See page 53, line 23 through page 54, line 2. The reference refers to Figure 8 as depicting the drug delivery. Referring to Figure 8, in response to stimuli, the site-specific conjugate within the endosome releases drug (D) from the conjugate, and drug (D) diffuses through the endosomal membrane and into the cell's cytosol. Figure 8 illustrates that the endosomal membrane remains intact during this process. The reference fails to describe a composition that is effective in disrupting the lysosomal membrane, or a method in which the lysosomal membrane is disrupted.

Furthermore, the invention now claimed recites that the transport agent is a polycarboxylic acid polymer selected from the group consisting of polyethylacrylic acid, polypropylacrylic acid, polybutylacrylic acid, and mixtures thereof. The reference describes the polymer useful in the site-specific conjugate as including a monomer such as acrylic acid and methylacrylic acid. Because the reference fails to describe the invention as now claimed, the reference is not anticipatory. Withdrawal of this grounds for rejection is respectfully requested.

Applicants further submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed.

The Rejection of Claims 34-37, 39, 41-52, 55-77,  
79, 81-90, 101, and 102 Under 35 U.S.C. § 103(a)

Claims 34-37, 39, 41-52, 55-77, 79, 81-90, 101, and 102 stand rejected under 35 U.S.C. § 103 as being unpatentable over WO 93/14142 or WO 97/09068. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

The Examiner states that, although the cited references do not teach the use of ethylacrylic acid, propylacrylic acid, and butylacrylic acid, the reference does teach the use of methylacrylic acid, and because ethylacrylic acid, propylacrylic acid, and butylacrylic acid are homologues of methylacrylic acid, the claim compositions and methods are obvious in view of these references. Applicants respectfully disagree.

Claims 34, 74, 101, and 102 have been amended. Claims 34 and 74 have been amended to recite that the polycarboxylic acid polymer is selected from the group consisting of polyethylacrylic acid, polypropylacrylic acid, polybutylacrylic acid, and mixtures thereof. Claims 101 and 102 have been amended by substituting the transition "comprising" with the transition "consisting essentially of." Each of these independent claims recites that the polycarboxylic acid is selected from the specified acids. Neither of the cited references teaches

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or suggests the use of these claimed acids. Applicants refer to the declaration of Dr. Stayton provided with Amendment A which applicants believe demonstrates that, although homologous, the recited polycarboxylic acids have properties that differ significantly from polyacrylic acid and polymethylacrylic acid, the polycarboxylic acids described in the cited references. The point of Dr. Stayton's declaration is simply to demonstrate that homologous polycarboxylic acids need not, and in fact do not, have the same properties. The fact that the recited polycarboxylic acids have properties that differ from one to the other does not negate the fact that the recited polycarboxylic acids have properties that differ from polyacrylic acid and polymethylacrylic acid of the cited references.

Furthermore, neither the cited references describes a composition or method that is effective in disrupting an endosomal membrane. Neither reference teaches, suggests, or provides any motivation to make a composition or employ a method that is effective in disrupting an endosomal membrane. The objective of each invention described in these references is attained without endosomal or lysosomal membrane disruption.

Because the cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, withdrawal of the rejection is respectfully requested.

The Rejection of Claims 60-63 Under 35 U.S.C. § 103(a)

Claims 60-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 93/14142 or WO 97/09068, further in view of U.S. Patent No. 5,876,989, issued to Berg. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claims 60-63 depend from Claim 34, which has been amended. Deficiencies of the teachings of WO 93/14142 or WO 97/09068 noted above are not cured by the teaching of the Berg reference. The Berg reference fails to teach or suggest a composition or method that

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includes a polymer carrier. None of the cited references describes a composition or method that includes one of the recited polycarboxylic acid polymers.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed. Withdrawal of the rejection is respectfully requested.

The Rejection of Claim 36 Under 35 U.S.C. § 103

Claim 36 stands rejected under 35 U.S.C. § 103 as being unpatentable over WO 93/14142 or WO 97/09068 in view of U.S. Patent No. 5,807,306, issued to Shapland. Withdrawal of this grounds for rejection is respectfully requested for the following reasons. Claim 36 depends from Claim 34, which has been amended. The deficiencies of the teachings of WO 93/14142 or WO 97/09068 noted above are not cured by the teaching of the Shapland reference. None of the cited references teaches or suggests a composition that is effective in disrupting an endosomal membrane, or a method in which the endosomal membrane is disrupted. None of the cited references describes a composition or method that includes any of the cited polycarboxylic acid polymers.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 53-56 Under 35 U.S.C. § 103(a)

Claims 53-56 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 93/14142 or WO 97/09068 in view of the Anderson reference. Withdrawal of this grounds for rejection is respectfully requested for the following reasons.

Claims 53-56 depend from Claim 34, which has been amended.

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The deficiencies of the teachings of WO 93/14142 or WO 97/09068 noted above are not cured by the teaching of the Anderson reference. None of the cited references describes a composition or method that includes any one of the recited polycarboxylic acid polymers.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed. Withdrawal of the rejection is respectfully requested.

#### CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 34-37, 57-69, 74-77, 101, and 102 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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